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(54) Title: PROCESS FOR THE PREPARATION OF FLUORO COMPOUNDS FROM THE CORRESPONDING AMINES

(57) Abstract

Compounds containing a primary amino group are converted into compounds containing a fluorine atom in place of the amino group by reaction of the amino compound with hydrogen fluoride and a nitrosating reagent under the influence of ultrasound or microwaves.

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PROCESS FOR THE PREPARATION OF FLUORO COMPOUNDS FROM THE CORRESPONDING AMINES

This invention relates to the preparation of fluoro compounds from amines by replacement of the amino group by a fluorine atom.

It is known to produce fluoro compounds from corresponding amines, particularly aromatic amines, by conversion of the latter into a diazonium tetrafluoroborate salt which is then decomposed thermally to produce the fluoro compound. It is also known to carry out the diazotization of aromatic amines in anhydrous hydrofluoric acid with subsequent heating to produce the corresponding fluoro compound. Neither of these methods is entirely satisfactory. The first involves isolation of the tetrafluoroborate salt which is hazardous and time consuming. The latter method gives poor yields when substituted aromatic amines are used, especially if the substitution is in the ortho position. Also, the reaction has to be carried out under pressure because anhydrous hydrofluoric acid is volatile.

There have been a number of proposals of methods for the production of fluoro compounds which are said to give improved results. For example, European Specification EP-A-0430434 (Imperial Chemical Industries plc.) describes a process for the preparation of fluoro aromatic and fluoro heteroaromatic compounds by reaction of corresponding aromatic or heteroaromatic amines with a

of 100 w to 5kW.

This process is applicable to a wide variety of amino group containing compounds including more particularly aromatic and heteroaromatic primary amines and alpha-amino acids.

The invention may be, for example, applied to aromatic amino-compounds of the formula

$$A(NH_2)_n$$

where A is an unsubstituted or substituted aromatic or heteroaromatic radical and n is an integer, e.g. from 1 to 4. A may be for example a residue of benzene, naphthalene, diphenyl, acenaphthene, fluorene, or pyrene or a heteroaromatic compound such as pyridine or quinoline.

The invention may also be applied to α-amino acids such as alanine, valine, phenylalanine, isoleucine, tyrosine, and threonine, and to aralkylamines such as phenylethylamine.

Examples of suitable aromatic and heteroaromatic amines which may be subjected to the process of the presentinvention may be represented by the general formula:

$$\begin{array}{c} NH_2 \\ | \\ Ar\text{-}(R)_n \end{array}$$

where Ar is phenyl, α- or β-naphthyl, pyridyl, quinolyl, thienyl, or diphenyl, n is 0, 1, 2 or 3 and R is halogen, alkyl, hydroxy, alkoxy, COOH, CHO, alkoxycarbonyl, nitro, cyano, trifluoromethyl, carbamoyl, alkylcarbamoyl,

nitrogen oxides.

In some cases improved yields are obtained by incorporating boron trifluoride etherate into the reaction mixture.

The amount of nitrosating reagent which is used in the process can be varied within wide limits. Preferably from 1.0 to 5.0, especially from 1.0 to 2.0 and more especially from 1.1 to 1.5, mole of nitrosating reagent is used per mole of primary amine.

The amount of hydrogen fluoride complex to primary amine can be carried within wide limits. Preferably 5 to 200, especially 10 to 50 and more especially 10 to 25, parts of liquid are used per part of primary amine.

The reaction may be carried out at any temperature in the range -20°C to +150°C, but it is preferably carried out at 0 to 70°C, and especially at 0 to 50°C. The pressure is not critical and it is ordinarily convenient to carry out the reaction at ambient pressure.

The ultrasound or microwaves may be provided using commercially available sources, e.g. an ultrasonic cleaning bath or a microwave oven. The frequency of the ultrasound should be chosen to maximise absorption of energy by the reaction medium. Typically, the ultrasound should have an intensity of at least 20, preferably 50, more preferably 100 and especially 200 W/cm^2. Microwaves should have a frequency of 300 MHz to 3GHz and a power of 200 W to 5kW. (In some countries, the maximum frequency is fixed by law.)

at 150-153oC @ atmospheric pressure. The distillation was complete in 45 minutes affording 1-fluoro-2,4,6-trimethylbenzene (2.1 g, 89.3%) as a colourless liquid.

The ^{1}H n.m.r. spectrum contained signals at δ_H ($CDCl_3$) 2.31, 2-CH_3 and 6-CH_3 (d, J=2.0 Hz, 6H); 2.32, 4-CH_3 (s, 3H); 6.88, 3-H and 5-H (d, J=7.0 Hz, 2H). The ^{19}F n.m.r. spectrum had a signal at δ_F ($CDCl_3$) 127.8, 1-F (s).

The mass spectrum produced a molecular ion at m/z 138 and the expected fragmentation pattern for 1-fluoro-2,4,6-trimethylbenzene at m/z 123, 109, 97, 91 and 83.

EXAMPLE 2

Diazotization of 2,6-dimethylaniline in Et_3N-3HF

The diazotization of 2,6-dimethylaniline (2.3 g, 0.02 mol) was performed under the same conditions as described for 2,4,6-trimethylaniline in Example 1. The reaction mixture turned yellow during the initial addition of sodium nitrite (2.0 g, 0.03 mol) and gradually turned red with the increased addition of sodium nitrite. Some tar was formed which was easily extracted with solvent. The work-up was identical to that described for 2,4,6-trimethylaniline. Diethyl ether (150 cm^3) was used for the extraction of the organic layer from the aqueous washings. The organic extract was dried over magnesium sulphate.

Fractional distillation of the solvent formed an orange oil which was distilled at 141-143oC @ atmospheric pressure affording 1-fluoro-2,6-dimethylbenzene (2.0 g,

liquid.

The ^{19}F n.m.r. spectrum had a signal at δ_F ($CDCl_3$) 121.9, 1-F (ddq, J=8.5 Hz, J=10.5 Hz and J=2.2 Hz). From the GC/MS the compound showed the expected molecular ion at m/z 124 and the expected fragmentation for 1-fluoro-2,5-dimethylbenzene at m/z 109, 101, 96, 83 and 77.

EXAMPLE 4

Diazotization of 2,4-dimethylaniline in Et_3N-3HF

A similar approach was used for the diazotization of 2,4-dimethylaniline as that described in Example 1. Addition of sodium nitrite (2.0 g, 0.03 mol) to 2,4-dimethylaniline (2.3 g, 0.02 mol), initially formed a yellow colour which eventually turned orange. Diazotization became evident after 20 minutes when the evolution of gas was vigorous. Very little undissolved sodium nitrite was detected at the end of the reaction.

Work-up as described in Example 1 for 2,4,6-trimethylaniline formed a brown oil on distillation of diethyl ether. Distillation of the oil at 143-144°C @ atmospheric pressure afforded 1-fluoro-2,4-dimethylbenzene (1.73 g, 74.6%) as a clear liquid.

The ^1H n.m.r. spectrum contained signals at δ_H ($CDCl_3$) 2.23, 2-CH_3 (d, J=1.8 Hz, 3H); 2.28, 4-CH_3 (s, 3H); 6.87, 6-H (t, J=9.0 Hz, 1H); 6.92, 5-H (ddd, J=8.0 Hz, J=5.5 Hz and J=2.0 Hz, 1H) and 6.97, 3-H (dm, J=7.8 Hz and J=2.0 Hz, 1H). The ^{19}F n.m.r. spectrum has a signal at δ_F ($CDCl_3$) 124.2, 1-F (complex m).

The mass spectrum produced a molecular ion at m/z

2,3-dimethylbenzene at m/z 109, 101, 96, 86, 83 and 77.

EXAMPLE 6

Diazotization of 3,4-dimethylaniline in Et_3N-3HF

3,4-Dimethylaniline (2.3 g, 0.02 mol) was added to Et_3N-3HF in proportions (0.15 g) over a 40 minute period at 0°C. Sodium nitrite (2.3 g, 0.03 mol) was added in small quantities (100 mg) under the influence of ultrasound. The slow addition of both substrates helped to reduce the formation of tar. After the complete addition of both substrates, the reaction vessel was allowed to warm to room temperature and ultrasound was applied for a further 10 minutes. The mixture was poured into water (100 cm^3). The organic layer was extracted with diethyl ether (150 cm^3 x 2) and dried over magnesium sulphate.

Fractional distillation of the solvent afforded a brown oil which was distilled at 138-139°C @ atmospheric pressure affording 1-fluoro-3,4-dimethylbenzene (1.30 g, 56.1%) as a clear liquid. Attempts were made to extract any material with a Soxhlet apparatus, but such measures did not improve the isolated yield of the product. The ^{19}F n.m.r. spectrum had a signal at δ_F ($CDCl_3$) 120.1, 1-F (dddq, J=6.0 Hz, J=9.6 Hz, J=8.6 Hz and J=1.0 Hz). From the GC/MS the compound showed the expected molecular ion at m/z 124 and the expected fragmentation for 1-fluoro-3,4-dimethylbenzene at m/z 109, 101, 97, 83 and 77.

EXAMPLE 8

Diazotization of 2-fluoroaniline in Et_3N-3HF

The diazotization of 2-fluoroaniline (2.3 g, 0.02 mol) was performed under the same conditions as those described for 4-fluoroaniline. Addition of sodium nitrite (2.0 g, 0.03 mol) caused the evolution of gas. The clear reaction mixture initially turned yellow and gradually darkened to a red colour. Some tar was formed during addition of sodium nitrite which was partially extracted with diethyl ether (30 cm^3). The reaction mixture was poured into water (150 cm^3) and extracted with diethyl ether (300 cm^3). The combined ether extracts were dried over magnesium sulphate and fractional distillation of the solvent afforded a red oil.

Distillation of the oil at 88-90°C @ atmospheric pressure afforded 1,2-difluorobenzene (1.32 g, 55.9 %) as a clear colourless liquid.

The i.r. spectrum contained major peaks at υ_{max} 3080 cm^{-1} (υ_{ArC-H}); 1620-1570 cm^{-1} ($\upsilon_{ArC=C}$) and 1401-900 cm^{-1} (υ_{C-F}) and the ^1H n.m.r. spectrum showed signals at δ_H ($CDCl_3$) 7.05-7.25 (complex m). The ^{19}F n.m.r. spectrum had a signal at δ_F ($CDCL_3$) 138.9, 1-F, 2-F (ddd, J=9.0 Hz, J=9.0 Hz and J=5.5 Hz).

The mass spectrum produced a molecular ion at m/z 114 and the expected fragmentation pattern for 1,2-difluorobenzene at m/z 94, 88, 81, 75, 70 and 63.

The mass spectrum produced a molecular ion at m/z 96 and the expected fragmentation pattern for fluorobenzene at m/z 92, 75, 70 and 63.

EXAMPLE 10

Preparation of 1,2-difluorobenzene in HF/THF with ultrasound

An FEP container was initially cooled to -78°C with acetone/Drikold and carefully charged with HF/THF (4:1). 2-Fluoroaniline (5.0 g, 0.05 mol) was added to the HF/THF mixture under vigorous stirring and allowed to warm to -10°C. When the desired temperature was reached the container was transferred to an ultrasonic bath containing an ice-salt water mixture. The container was fitted with a Drikold condenser adapted with a polypropylene filter funnel.

Sodium nitrite (4.95 g, 0.07 mol) was added over 35 minutes under the influence of ultrasound. During the addition an exothermic reaction occurred with the evolution of a brown gas. The ultrasound was applied for a further 1 hour after the complete addition of sodium nitrite at room temperature. The mixture was further heated for 1 hour at 45°C under the influence of ultrasound. Dediazoniation was complete after 1 hour. The mixture was poured onto iced water (150 cm^3). The organic constituents were extracted with dichloromethane (200 cm^3 x 2). The extracts were finally washed with water (100 cm^3), stirred with sodium fluoride (2.5 g) and dried with magnesium sulphate for 12 hours.

atmospheric pressure afforded to clear liquid of 1,4-difluorobenzene at 87-88oC (3.16 g, 62.0 %). Without ultrasound, the yield is only 40%.

EXAMPLES 12 AND 13

The addition of BF_3-etherate complex has helped to improve the yield of isolated 1,2-difluorobenzene and 1,4-difluorobenzene as shown below.

Substrate	Product	Yield %	Conditions
2-fluoroaniline	1,2-difluorobenzene	60	$NaNO_2$, BF_3 etherate with ultrasound
4-fluoroaniline	1,4-difluorobenzene	68	$NaNO_2$, BF_3 etherate with ultrasound

The procedures used for these reactions are similar to Examples 10 and 11. 5 cm^3 of the BF_3 etherate complex were used.

EXAMPLES 14, 15 and 16

Proceeding as in Example 1, the following α-amino acids were converted into the corresponding α-fluoroacids in the stated yields:

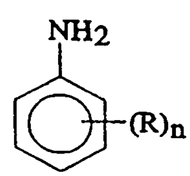
Example 14	β-alanine	50%
Example 15	DL-Valine	75%
Example 16	L-phenylalanine	70%

CLAIMS

1. Process for converting a compound containing a primary amino group into a compound containing a fluorine atom in place of said amino group which comprises contacting said amino-group-containing compound with hydrogen fluoride, or with a complex thereof with a base, and a nitrosating reagent at a temperature in the range -20° to +150°C while subjecting the reagents to the action of ultrasound having a frequency of 10 to 100 kHz and an intensity of at least 20 Watts/cm^2 or to the action of microwaves having a frequency of 300 MHz to 3GHz and an intensity between 100W and 5kW.

2. Process according to claim 1 wherein the amino-group-containing compound in an aromatic or heteroaromatic primary amine or an α-amino-acid.

3. Process according to claim 1 wherein the amino-group-containing compound is a compound of formula



where n is 0, 1, 2 or 3 and the radicals R, which may be the same or different when n is 2 or 3, are each halogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkylthio of 1 to 4 carbon atoms, carboxy, alkoxycarbonyl with 1 to 4 carbon atoms in the alkoxy, nitro, cyano or trifluoromethyl.

4. Process according to any one of claim 1 to 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01201

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07B39/00 C07C17/093 C07C25/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07B C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 110, no. 3, 16 January 1989 Columbus, Ohio, US; abstract no. 023510, YONEDA N ET AL: "Preparation of aromatic fluorides by photochemical diazotization and decomposition of aromatic amines" XP002034108 see abstract & JP 63 188 631 A (MITSUBISHI KASEI CORP.;JAPAN) 4 August 1988 ---	1
A	EP 0 467 742 A (RHONE POULENC CHIMIE) 22 January 1992 see claims ---	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/01201

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0467742 A	22-01-92	FR 2664588 A	17-01-92
		FR 2664589 A	17-01-92
		JP 4244049 A	01-09-92
		US 5354439 A	11-10-94
US 3481850 A	02-12-69	NONE	
CH 141750 A		NONE	

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